The Preparation of Some Piperidine Derivatives by the Mannich Reaction

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The Preparation of Some Piperidine Derivatives by the Mannich Reaction

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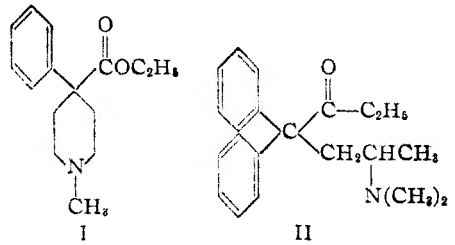
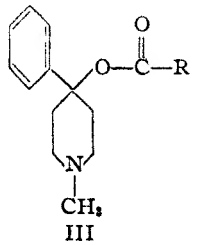
Demerol (I) and amidone (II) are of interest because of their marked analgesic action.[1] Esters of



I

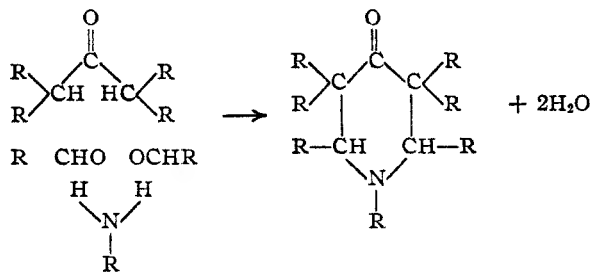
II



III

the 4-phenyl-4-piperidinols (III) also have analgesic properties.[2]

A number of piperidones have been prepared by the Mannich reaction.[3] It should be possible to extend the use of this reaction for the synthesis of a large variety of 4-piperidones with different substituents in the 1,2,3,5 and 6 positions.



The usual procedure for reaction is to reflux an aqueous or alcoholic solution of the ketone, aldehyde and amine, or amine hydrochloride. Attempts to repeat these preparations and to extend them were discouraging because of poor yields and difficulty in isolating pure products.

Recalling that it is not piperidine that catalyzes the Knoevenagel reaction but piperidine salts of carboxylic acids,[4] it was thought that the Mannich reaction might be more successful using acetic acid rather than water or alcohol as a solvent. The amine acetate might catalyze the reaction, it would dissociate more readily into the amine than would the amine hydrochloride, and the temperature of the reaction could be raised without loss of the gaseous amines, which was not the case when an alcoholic solution of the amine was used. Accordingly glacial acetic acid was tried as a solvent and reaction took place rapidly, the isolation of pure products was easy, and the yields were very satisfactory.

Some of the piperidones were reduced catalytically and others were condensed with phenylmagnesium bromide, to give secondary and tertiary 4-piperidinols. The secondary piperidinols were converted to esters. The ketones, alcohols and esters are being tested for pharmacological activity.

(1) Scott, Robbins and Chen, *Science*, **104**, 587 (1946).

(2) Jensen, Lindquist, Rekling and Wolffbrandt, *Dansk. Tidsskr. Farm.*, **17**, 173 (1943); *C. A.*, **39**, 2506 (1945); Lee and co-workers, *J. Org. Chem.*, **12**, 894, 904, 911 (1947).

(3) Blicke, "The Mannich Reaction," "Organic Reactions," **1**, 303 (1942).

(4) Kuhn, Badstübner and Grundmann, *Ber.*, **69**, 98 (1936).

Experimental

Procedure for the Mannich Condensation.—In general, 0.2 mole of the amine or of ammonium acetate was dissolved in 20 cc. of glacial acetic acid, and 0.4 mole of aldehyde and 0.2 mole of ketone added to this solution. The mixture was heated to the boiling point and then allowed to cool to room temperature. When the product separated as a crystalline solid on cooling, it was filtered, washed and recrystallized. The free bases were converted to the hydrochlorides either by the addition of concentrated hydrochloric acid or by passing hydrogen chloride into an ether solution of the base. When an oil separated, the base was converted directly to the hydrochloride and purified by crystallization. The hydrochloride was converted to the free base by adding aqueous ammonia to an alcohol solution, and the base precipitated by dilution with water.

Although the molar ratio of amine:aldehyde:ketone usually was 1:2:1 as required by the equation, it frequently was desirable to reduce the amount of the aldehyde since in some cases the unreacted aldehyde interfered with the purification of the product. The per cent. yield was calculated from the amount of aldehyde taken for the reaction. The results are summarized in Table I. It should be stated that the conditions for preparing and isolating these compounds are not necessarily the optimum. The object of the present investigation was merely to obtain a sufficient quantity of the desired product.

Reduction of Piperidone to Piperidinols and Conversion to Esters.—A solution of 6.5 g. (0.02 mole) of the 1,3,5-trimethyl-2,6-diphenyl-4-piperidone hydrochloride (No. 13 of Table I) in 15 cc. of 95% ethyl alcohol was shaken with hydrogen in the presence of 0.2 g. of platinum oxide catalyst at 45 pounds pressure until the calculated amount of hydrogen was absorbed. After removal of the catalyst an excess of aqueous ammonia was added and the free base precipitated by dilution with water. Crystallization from methyl alcohol gave 5.5 g. (91%), m. p. 133–135°.

Anal. Calcd. for $C_{20}H_{25}NO \cdot H_2O$: C, 76.64; H, 8.68. Found: C, 76.80; H, 8.42.

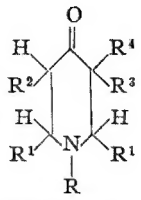
The **hydrochloride** was prepared by passing hydrogen chloride into an ether solution of the free base. Crystallization from methyl alcohol gave a product that did not melt below 300°.

Anal. Calcd. for $C_{20}H_{26}ClNO$: Cl, 10.68. Found: Cl, 10.75.

The alcohol was converted into various esters by reaction with the required acid anhydride in pyridine solution. The **acetate** melted at 198–200°.

TABLE I

SUBSTITUTED 4-PIPERIDONES PREPARED BY THE MANNICH REACTION



No.	R	R¹	R²	R³	R⁴	Yield,[a] %	Free bases[b] M. p., °C.	Formula	Analyses,[d] % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Hydrochlorides[c] M. p., °C.	Analyses, % Cl[e] Calcd.	Found
1	H	C_6H_5	H	H	CH_3	40	86–87	$C_{18}H_{19}NO$	81.46	81.81	7.22	7.16	224–226	11.77	11.98
2	H	C_6H_5	H	CH_3	CH_3	57[f]	114–115	$C_{19}H_{21}NO$	81.68	81.32	7.57	7.59	201–202	11.23	11.36
3	H	C_6H_5	H	H	$CH(CH_3)_2$	20[g]	125–126	$C_{20}H_{23}NO$	81.87	81.60	7.72	7.78	192–194	10.75	10.63
4	H	C_6H_5	CH_3	H	CH_3	75[g]	131–133	$C_{19}H_{21}NO$	81.68	81.84	7.57	7.30	228–230	11.23	11.48
5	H	C_6H_5	C_2H_5	H	C_2H_5	48		$C_{21}H_{25}NO$	Not obtained crystalline				219–221	10.31[g]	10.46[g]
6	H	4-$CH_3OC_6H_4$	CH_3	H	CH_3	62	124–125	$C_{21}H_{25}NO_2$	74.31	74.86	7.42	7.55	234–235	9.43	9.53
7	H	3-CH_3O-4-HOC_6H_3	CH_3	H	CH_3	68[g]	169–170	$C_{21}H_{25}NO_3$	67.91	64.33[f]	6.79	6.85[f]	228–229	8.70	8.91
8	H	3,4-$(CH_3O)_2C_6H_3$	CH_3	H	CH_3	62[g]	130–131	$C_{23}H_{29}NO_3$	69.12	69.45	7.32	7.36	202–203	8.14	8.12
9	H	3,4-$(CH_2O_2)C_6H_3$	CH_3	H	CH_3	46[g]	172–174	$C_{21}H_{21}NO_3$	68.65	68.75	5.76	5.62	222–224	8.78	8.78
10	CH_3	C_6H_5	H	H	CH_3	40[g]	130–131	$C_{19}H_{21}NO$	81.68	81.58	7.57	7.53	167–168	11.22	11.29
11	CH_3	C_6H_5	H	CH_3	CH_3	13	131–132	$C_{20}H_{23}NO$	81.87	81.29	7.72	7.84	195–196	10.75	10.81
12	CH_3	C_6H_5	H	H	$CH(CH_3)_2$	26	109–110	$C_{21}H_{25}NO$	82.04	82.00	8.20	8.04	197–199	10.31	10.57
13	CH_3	C_6H_5	CH_3	H	CH_3	50	91–92	$C_{20}H_{23}NO$	81.87	82.12	7.72	7.81	222–224	10.75	10.74
14	CH_3	C_6H_5	C_2H_5	H	C_2H_5	30	110–111	$C_{22}H_{27}NO$	82.20	82.03	8.47	8.28	198–199	9.91	9.81
15	CH_3	C_6H_5	$COOC_2H_5$	H	$COOC_2H_5$	?	92–93[h]	$C_{26}H_{27}NO_5$					196–199		
16	CH_3	4-$CH_3OC_6H_4$	CH_3	H	CH_3	18	132–134	$C_{22}H_{27}NO_2$	74.76	74.89	7.70	7.46	209–210	9.09	9.12
17	CH_3	3,4-$(CH_3O)_2C_6H_3$	CH_3	H	CH_3	26	148–149	$C_{24}H_{31}NO_5$	69.71	70.52	7.56	7.72	166–167	7.88	7.74
18	CH_3	3,4-$(CH_2O_2)C_6H_3$	CH_3	H	CH_3	47	69–75	$C_{23}H_{23}NO_5$	69.25	69.89	6.08	5.86	228–229	8.49	8.54
19	C_2H_5	C_6H_5	CH_3	H	CH_3	6	135–136	$C_{21}H_{25}NO$	82.04	82.02	8.20	8.14	206–207	10.31	10.26
20	$C_6H_5CH_2$	C_6H_5	H	H	CH_3	18	103–104	$C_{25}H_{25}NO$	84.44	84.75	7.09	7.29	157–159	9.05	9.11

[a] The molar ratio of amine:aldehyde:ketone was 1:2:1 for nos. 1, 5, 7, 8, 9, 13, 14, 15, 16, and 20; 1.5:2:1 for nos. 2, 4, and 6; 1:1.5:1 for nos. 3, 10, 11, and 12; 1:1:1 for nos. 17, 18, and 19. Nos. 1, 2, 4, 5, 6, 7, 9, 13, and 19 were brought to the boiling point of the solution and then allowed to stand at room temperature overnight. Nos. 3, 8, 10, 11, and 12 were heated to 100° and allowed to stand overnight. Nos. 15, 16, and 17 were allowed to react at room temperature for twenty-four hours, nos. 14 and 18 for forty-eight hours and no. 20 for seventy-two hours. [b] Nos. 2 and 6 were crystallized from ethyl alcohol, nos. 7, 15, and 17 from *n*-propyl alcohol, no. 8 from aqueous *n*-propyl alcohol, and no. 3 from a mixture of methyl alcohol and ethyl acetate. The remainder were crystallized from methyl alcohol. [c] Nos. 1, 5, 6, 12, and 16 were crystallized from a mixture of methyl alcohol and ethyl acetate, no. 2 from ethyl acetate–ether, nos. 3, 4, 7, 14, 15, 19, and 20 from methyl alcohol, no. 10 from ethyl acetate, no. 11 from methyl alcohol–ethyl acetate–ether, no. 13 from aqueous methyl alcohol and no. 18 from ethyl alcohol; nos. 8 and 9 were precipitated from acetic acid solution and no. 17 from methyl alcohol solution by the addition of ether. [d] Micro carbon–hydrogen analyses by Mr. C. W. Koch, Albany, California. Volumetric determination of chloride ion by V. B. [e] Isolated as free base. [f] Calcd. for monohydrate: C, 64.76; H, 7.00. [g] Calcd.: C, 73.34; H, 7.62. Found: C, 73.38; H, 7.05. [h] Petrenko-Kritschenko and Lewin, *Ber.*, **40**, 2882 (1907), reported 86°.

TABLE II

4-PHENYL-4-PIPERIDINOL HYDROCHLORIDES AND FREE BASES

Piperidone reduced, no.	Hydrochlorides Yield, %	M. p., °C.	Analyses, % Cl Calcd.	Found	Free bases M. p., °C.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
4	72	223–235	9.00	9.12	137–139	$C_{19}H_{23}NO$	83.97	84.32	7.62	7.41
6	82	212–215	7.81	7.84	133–135	$C_{21}H_{27}NO_3$	77.68	77.93	7.49	7.50
10	98	260–262	9.00	8.78	155–156	$C_{19}H_{23}NO$	83.97	84.06	7.62	7.82
11	75	262–265	8.69	8.56	197–199	$C_{20}H_{25}NO$	84.06	83.83	7.87	8.38
13	95	307–309	8.69	8.59	235–237	$C_{20}H_{25}NO$	84.06	84.09	7.87	7.89

Anal. Calcd. for $C_{22}H_{27}NO_2$: C, 78.30; H, 8.07. Found: C, 78.12; H, 7.94.

The **acetate hydrochloride** did not melt below 300°.

Anal. Calcd. for $C_{22}H_{28}ClNO_2$: Cl, 9.48. Found: Cl, 9.54.

The **propionate** melted at 151–153° and was converted to the **hydrochloride**, m. p. 263–266°.

Anal. Calcd. for $C_{23}H_{30}ClNO_2$: Cl, 9.14. Found: Cl, 9.23.

The ***n*-butyrate** melted at 124–125° and was converted to the **hydrochloride**, m . p. 248–250°.

Anal. Calcd. for $C_{24}H_{32}ClNO_2$: Cl, 8.82. Found: Cl, 8.97.

The reduction of 1,3,5-trimethyl-2,6-di-*p*-anisyl-4-piperidone (no. 16 of Table I) by the above procedure gave the piperidinol, m. p. 142–144.5°.

Anal. Calcd. for $C_{22}H_{29}NO_3 \cdot H_2O$: C, 70.73; H, 8.38. Found: C, 70.74; H, 8.14.

The **hydrochloride** melted at 246–251°.

Anal. Calcd. for $C_{22}H_{30}ClNO_3$: Cl, 9.05. Found: Cl, 9.18.

The alcohol was converted into the acetyl and propionyl derivatives by reaction with the required anhydride in pyridine solution. The **acetate** melted at 222–226°.

Anal. Calcd. for $C_{24}H_{31}NO_4$: C, 72.50; H, 7.86. Found: C, 73.07; H, 7.76.

The **acetate hydrochloride** melted at 256–257° with decomposition.

Anal. Calcd. for $C_{24}H_{32}ClNO_4$: Cl, 8.17. Found: Cl, 8.26.

The **propionate** melted at 171–173° and was converted to the **hydrochloride**, m. p. 260–262°.

Anal. Calcd. for $C_{25}H_{34}ClNO_4$: Cl, 7.92. Found: Cl, 7.81.

4-Phenyl-4-piperidinols.—A solution of 0.05 mole of the piperidone in ether was added to twice the calculated amount of an ether solution of phenylmagnesium bromide at 0°, and the mixture refluxed for one-half hour. The mixture was cooled to 0°, and a solution of 10 cc. of concentrated hydrochloric acid in 20 cc. of water was added slowly with stirring. The hydrochloride of the piperidinol crystallized and was removed by filtration, washed with ether, and crystallized from a suitable solvent. The free bases were prepared by adding aqueous ammonia to an alcohol solution of the hydrochloride, and were crystallized from methyl alcohol. The data on the individual compounds are summarized in Table II.

Summary

Twenty substituted 4-piperidones have been prepared by the Mannich reaction using acetic acid as a solvent. Two of the piperidones have been reduced to the 4-piperidinols, and the acetates, propionates and butyrates have been prepared. Five of the piperidones have been converted to 4-phenyl-4-piperidinols by reaction with phenylmagnesium bromide. All of the compounds are being tested for possible pharmacological activity.

STANFORD UNIV., CALIFORNIA RECEIVED MAY 3, 1948

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

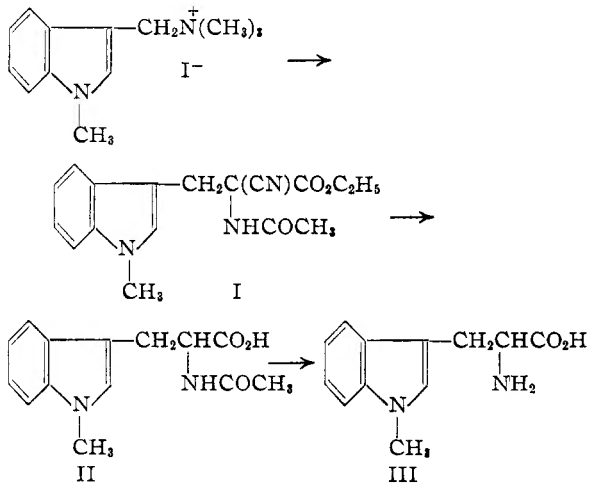
A Synthesis of 1-Methyltryptophan[1]

BY H. R. SNYDER AND ERNEST L. ELIEL[2]

In previous communications[3] the synthesis of 1-methylgramine and an alkylation reaction by its methiodide were described. The alkylating properties of 1-methylgramine methiodide have now been adapted to the synthesis of 1-methyltryptophan. This synthesis is of interest not only because it furnishes another instance of a facile alkylation by a quaternary salt which cannot react through an elimination mechanism,[3,4] but also because of the possible action of the product as an antimetabolite.

1-Methyltryptophan was obtained by alkylation of the sodium salt of ethyl acetamidocyanoacetate[5] with 1-methylgramine methiodide and hydrolysis of the alkylation product (I, 69% yield) with aqueous alkali. When 15% sodium hydroxide was employed in the hydrolysis, about half of the product was obtained as the free amino acid (III) and about half as the acetyl derivative (II). By subsequent hydrolysis of the acetyl derivative with 20% sodium hydroxide the conversion of the alkylation product to the free amino acid was brought to 92%. Hydrolysis of (I) with 10% alcoholic potassium hydroxide converted it only to the acetyl derivative (II).

A synthesis of 1-methyltryptophan has been reported in connection with investigations into the chemical nature of certain toad poisons.[6] The product, which was obtained by an azlactone synthesis from 1-methylindole-3-aldehyde, is stated to melt at 289° with decomposition. Our product melts at 223–225° with decomposition. Because of this discrepancy it was considered necessary to prove the structure of the 1-methyltryptophan obtained by the alkylation reaction. Accordingly, this amino acid was decarboxylated by heating in molten diphenylamine at 240–250° (a method which has been applied to the synthesis of tyramine from tyrosine).[7] The product was 1-methyltryptamine, identified as its hydrochloride, picrate and phthalimide. A by-product of the decarboxylation had the composition of a diketopiperazine related to 1-methyltryptophan.



We are at present unable to explain the difference in the melting points of the methyltryptophans obtained by the two different methods.

Experimental[8,9]

α-Carbethoxy-α-acetamido-β-3(1-methyl)-indolepropionitrile (I).—To the solution prepared from 1.15 g. of

(1) Presented before the Organic Division at the 113th meeting of the American Chemical Society, Chicago, Illinois, April, 1948.

(2) Present address: University of Notre Dame, Notre Dame, Indiana.

(3) Snyder and Eliel, THIS JOURNAL, **70**, 1703, 1857 (1948).

(4) Albertson, *ibid.*, **70**, 669 (1948).

(5) Tullar, U. S. Patent 2,393,723; *C. A.*, **40**, 2465[5] (1946).

(6) Wieland, Konz and Mittasch, *Ann.*, **513**, 1 (1934).

(7) Abderhalden and Gebelein, *Z. physiol. Chem.*, **152**, 125 (1926).

(8) All melting points are corrected.

(9) Microanalyses by Mr. Howard Clark.